Remarks

Claims 1-10, 12, 14-18, 20-26, 28 and 30-41 are pending in the present application. The following objections and rejections are at issue and are set forth by number in the order in which they are addressed:

1. Claims 1-10, 12, 14-18, 20-26, 28 and 30-41 are provisionally rejected for double patenting over co-pending Application No.: 11/928,464 in view of Schroder;
2. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al.;
3. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al., in view of Schroder et al.;
4. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Primus et al. and Kolb et al.;
5. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Naldini et al.

The rejections listed above are addressed in order below.

1. Double patenting.

Applicants will file a terminal disclaimer if needed when the other issues are resolved.

2. The claims are not obvious over Mathor in view of each of Burns, Felts; Schott; and Persons

Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as

allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. Applicants respectfully traverse.

At page 7, the Examiner states that Mathor et al. teach that protein expression is directly proportional to integration events (i.e., copy number)(p. 10376, column 1). The Examiner goes on to state that:

> "It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. and Burns et al. by serially transducing their cells with high MOIs (such as MOIs of 1,000) to achieve the claimed ranges of integration events, with a reasonable expectation of success. The motivation to do so is provided by Mathor et al., who teach the possibility of specifying the level of transgene expression by controlling the integration events (Abstract, p. 10376, column 1).

Office Action, p. 8. The Examiner cites the abstract and p. 10376 of Mathor. Mathor et al. state in this section that "The rate of secretion of the exogenous protein by cultures generated by single clones was proportional to the number of integrations per progenitor cell."

In the previous response and Fourth Declaration by Dr. Greg Bleck, Applicants presented evidence that the Examiner's assumption underpinning the rejection were not based on sound scientific reasoning. The Examiner addresses the previous Declaration at pages 13-14 of the Office Action. The Examiner states:

> The applicant argues that the fact that different clones can produce different amounts of protein has no relevance to whether a person of skill in the art would modify Mathor and make clones with 20 or more integrated retroviral vectors. This is not found persuasive. On the contrary, such knowledge in the art does have relevance to whether one of skill in the art would make clones with 20 or more integrated retroviral vectors. **The argument that the data in Table 1 of Mathor et al., which is limited to a maximum of 15 integrations cannot be extrapolated to a situation where there are 20 integrations is just an argument not supported by any evidence.** Based on the teachings in the prior art (including Liu, Stamps, and Mathor et al.), one of skill in the art would have known that protein production is proportional to the number of integrated copies and that retroviral insertion is random and that expression level is dependent on the insertion sites; therefore, one of skill in the art would not conclude that the data in Table 1 indicates a maximum of 15 integrations. Based on the teachings in the art as a whole, one of skill in the art would have had reasonably expected that clones comprising more than 15 integrations would express higher amounts of protein and would have known to look for several clones having higher integration numbers and select the high producer clones.

(Emphasis added). These statements by the Examiner have been addressed in the Fifth Bleck Declaration, which accompanies this response. The Examiner states that the Applicants arguments are not supported by any evidence. Applicants respectfully disagree. Evidence was provided in the Fourth Bleck Declaration. In order to advance the prosecution of this application, Dr. Bleck has provided an additional Declaration (the "Fifth Bleck Decl.") that is intended to clarify the evidence previously presented.

The following evidence supports the Applicants position that a person of skill in the art would not have been motivated to make cell lines containing 20 to 100 copies of an integrated retroviral vector for production of a protein of interest. Below, Applicants specifically establish facts that show why the Examiner's assumptions and statements concerning Mathor, Lui, Stamps and the other cited prior art are not supported by the references cited. These facts rebut the arguments and/or factual finding that have been developed by the Examiner. The rejections of the claims cannot stand without specially addressing and considering his rebuttal evidence.

The Bleck Declaration specifically addresses the cited prior art references. The cited references provide the following evidence and facts.

- Mathor et al. does not contain any data or any statement that the level of transgene expression can be controlled by controlling integration events within the range of 20 to 100 integrations. See Mathor et al. in its entirety, Fifth Bleck Decl. ¶5.
- Mathor et al. presents the data on proviral integration and transgene expression on p. 10373 and in Table 1. Fifth Bleck Decl. ¶5.
- This data shows increasing transgene expression as the proviral integrations increase from 1 to 8. When the number of proviral integrations increases to 15, the transgene expression actually decreases to a level lower than was observed with 8 integrations. Id.
- Mathor et al. teaches that transgene expression correlates with number of integrations over the range of 1 to 8 integrations. Id.
- Transgene expression decreased when a cell line with 15 integrations was analyzed. Id.
- Mathor's statement that "The rate of secretion of the exogenous protein by cultures generated by single clones was proportional to the number of integrations per progenitor cell" is valid with respect to the range of 1 to 8 integrations and does not apply outside

of that range. Id.

- The Examiner's attempt to apply the statement outside of the range is not factually supported, i.e., supported by the data. Fifth Bleck Decl. ¶5.
- The experiments in Mathor et al. were not conducted in a manner so that a statistical analysis could be conducted. See Mathor et al., particularly p. 10373, Fifth Bleck Decl. ¶7.
- The groups were not replicated and there is no way to determine experimental error. Id.
- Thus, it is not possible to construct a curve or equation from the data so that a correlation of transgene expression to a number of integrations outside of the data range (i.e., 20 to 100 integrations) can be made. Id.
- Any attempt to correlate the data from Mathor, which is based on unreplicated results with from 1 to 15 integrations, to the claimed 20 to 100 integrations is speculation without a factual basis. For example, based on the data in Mathor, it is speculation as to whether another clone with 15 integrations would have a level of transgene expression that is higher or lower than the reported clone. The reason for this is that the data is not amenable to statistical analysis so that such a prediction can be made. Id.
- None of the other references relied on by the Examiner teach a correlation of transgene expression to integration number in the claimed range of 20 to 100 retroviral integrations. Fifth Bleck Decl. ¶6.
- Schott et al. teaches a correlation over the range of 1 to 9 integrations. See Schott p. 304, Fig. 9; Fifth Bleck Decl. ¶6.
- The increase between 4 and 5 integrations and 6 and 7 integrations is much greater than the increase between 7 and 9 integrations. Id.
- This is similar to the Mathor et al. data and indicates that transgene expression levels off as opposed to continuing to increase, although, predications outside of the data range cannot be validly made. Id.
- Furthermore, Lui et al. contains data on the correlation of expression of transgenes separated by an IRES and does not address transgene expression correlated to number of integrations. See Lui Abstract, Fig. 2, Gig. 4, Fig. 5; Fifth Bleck Decl. ¶7
- Stamps et al. examined the role of the T-antigen gene and its site of integration in human

epithelial cell immortalization. See Stamps, p. 871, Col. 2, first full para., Fifth Bleck Decl. ¶7

- The cells examined had up to five integrations. Id.
- Stamps et al. does not comment on a correlation of transgene expression to number of integrations. Id.
- Persons et al., is directed to packaging cell lines for the production of infectious retroviral vectors, and thus is not relevant to using retroviral vectors to transduce cells to make a protein of interest. Persons et al. does not address protein production or the impact of including multiple copies of a retroviral vector in a cell line for protein production. See Persons et al., Abstract, Fourth Bleck Decl. ¶9.

These are the facts that Applicants are relying on to rebut the Examiner's arguments and assumptions concerning the cited prior art references. These facts establish that the Examiner's assumptions based on the prior art are not supported by the cited references and thus do have a rational underpinning. A primary step in the obviousness analysis is to "determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). A rejection for obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion." *Id.*, *quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The proper question to ask is whether a person of ordinary skill in the art would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424.

The Court also noted that:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added). The facts above establish that the Examiner's reasoning is not based on a rational underpinning. The data contained in Mathor cannot be applied outside of the

observed range of 1 to 15 integrations. See Bleck Decl. ¶7. The data points were not replicated and a curve cannot be constructed or fitted to the data to make any type of prediction outside of this range. Id. The observed data point at 15 integrations actually shows lower expression than was observed at 8 integrations. Id. This is the reason why the Examiner is incorrect in arguing that "one of skill in the art would have had reasonably expected that clones comprising more than 15 integrations would express higher amounts of protein and would have known to look for several clones having higher integration numbers and select the high producer clones." The data in Mathor et al. is not amenable to this assumption. Id. Because the experiments were not replicated and because there is not data on multiple clones with 15 (or a similar number) of integrations, it is not possible to predict or comment on the amount of expression one could expect from another clone with 15 integrations. Id. The single clone reported in Mathor et al. could be an example of the upper limit of expression, the median level of expression, or a low level of expression. Id. The fact is, without additional data, one cannot know whether other clones with 15 integrations would have higher levels of expression than the observed clone. Id. All that one knows for sure is the fact that the Mathor et al. data shows that expression from the clone with 15 integrations was lower than the expression observed in the clone with 8 integrations. Id.

Moreover, the *KSR* Court also recognized that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *KSR* at 1739-40 (*citing United States v. Adams*, 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966)). In his Fourth Declaration, Dr. Bleck provided evidence showing that at the time of the invention, the state of the art was that methylation of integrated retroviral vectors posed serious limitations on the use of the vectors for expression of transgenes. Fifth Bleck Decl., ¶ 8. In response, the Examiner states:

> The applicant argues that many of the references cited by Bestor and those included in Paragraph 4 of the fourth Declaration describe silencing in vitro due to methylation. This is not found persuasive for the same reasons as above. Specifically, the prior art teaches that methylation is dependent on the integration site, i.e., consistent with the teachings of Liu, Stamps, and Mathor et al. that expression level is dependent on the insertion sites. Gunzburg et al. (The EMBO Journal, 1984, 3: 1129-1135) teach that retroviral integration is random and take place either in active (i.e., the virus is expressed) or in inactive (i.e., the virus is not expressed) chromatin domains

> (see p. 1129, paragraph bridging columns 1 and 2, p. 1133, column 2, p. 1134, column 1). Based on these teachings, one of skill in the art would have known that the same number of integrations would result in different expression levels, depending on the insertion site. Furthermore, the prior art teaches that the expression and stability of the gene of interest directly correlates with the number of integrated retroviral vectors (see Schott et al. above). One of skill in the art would have known to look for clones comprising high numbers of integrated retroviral vectors and select the ones capable of producing high amounts of protein.

Office Action, p. 15.

Thus, the Examiner relies on Gunzburg et al. to rebut the facts contained in the Fourth Bleck Declaration. Gunzburg et al., which was published in 1984, addresses methylation of "multiple endogenous mouse mammary tumour virus (MMTV) proviral genes" that "are present at different locations in mouse inbred strains." See Abstract, Fifth Bleck Decl., ¶ 8. Gunzburg et al. finds that the methylation patterns are location and tissue specific and that the patterns are stably inherited and appear to be conferred upon the viral DNA by the flanking mouse genomic DNA. Id.. The authors state that "upon integration the provirus assumes the methylation pattern of the DNA into which is integrates." p. 1129, col. 1., p. 133, col. 2, Fifth Bleck Decl., ¶ 8. Importantly, Gunzburg et al. does not contain data or comments that address any correlation of methylation to expression of genes. Fifth Bleck Decl., ¶ 8. Just as important, Gunzburg et al. addresses endogenous proviral sequences and not the introduction of exogenous vectors containing transgenes. Fifth Bleck Decl., ¶ 8 These proviral sequences are endogenous to the genome and have been acquired at some point in the distant past. Fifth Bleck Decl., ¶ 8 Gunzburg et al. has very little relevance to the present invention or to the evidence previously submitted by Dr. Bleck.

Dr. Bleck goes on to specifically describe findings from scientific papers that contain evidence that is specific to the claims and which support the Applicants position that one of skill in the art would not have modified the prior art to make cell lines with the claimed 20 to 100 integrated retroviral vectors. The following findings of fact are supported by these references:

- Bestor and Tycko 1996 (attached at Tab 1 to the Fifth Bleck Decl.), identify two hypothetical roles of genomic methylation patterns. The first is a role of programmed demethylation and methylation during development. Fifth Bleck Decl., ¶ 8; Bestor p.

363, col. 1. The second role is that cytosine methylation is part of a genome defense system which inactivates parasitic sequences such as transposable elements and proviral DNA (i.e., integrated retroviruses). Fifth Bleck Decl., ¶ 8; Bestor p. 363, col. 1.

This second role of methylation is directly relevant to the present invention which utilizes high levels of integrated retroviral vectors. Fifth Bleck Decl., ¶ 8. Bestor and Tycko explain this relevance:

> The host defense hypothesis requires that the silencing apparatus recognize and inactivate parasitic sequence elements. Nearly all transposition and viral integration intermediates share certain structural features, and some satellite DNA is thought to undergo amplification by extrachromosomal rolling circle replication followed by insertion of the array into the genome. Recognition and de novo methylation of CpG sites in and around features characteristic of integration reactions would insure the inactivation of the invasive element immediately upon its integration. DNA methyltransferase may have an intrinsic ability to recognize integration intermediates that are characteristic of the above integration events. The de novo sequence specificity of mammalian DNA methyltransferase is strongly dependent on alternative secondary structures in DNA; four-way junctions in cruciform structures formed by inverted-repeats in supercoiled-plasmids are especially favored targets, as are secondary structures in artificial oligonucleotide substrates. This biochemical property suggests that invasive sequences might be targeted for de novo methylation because of their presentation of alternative secondary structures during integration (Fig la).

(Fifth Bleck Decl., ¶ 8; Bestor p. 364, col. 2, Citations omitted).

Thus, it was a concern that due to the nature of retroviral integration, the retroviral vectors would be targeted for inactivation by methylation. Increasing copy number enhances this problem. "A common characteristic of invasive sequences is their presence in multiple copies, and it has recently become known that repeated sequences can interact so as to trigger their mutual silencing." Fifth Bleck Decl., ¶ 8; Bestor p. 364, col. 2. Bestor and Tycko further address retroviral vectors:

> Retroviral vectors that transducer reporter genes or therapeutic agents have been observed to undergo methylation silencing after variable periods of expression in

> animals. Susceptability to de novo methylation and silencing has limited the usefulness of retroviral vectors in the construction of transgenic mouse lines, and it is probable that silencing phenomena may emerge as barriers to long term somatic gene therapy in humans. Successful gene transfer may require development of delivery vectors that evade the silencing response.

Bestor, p. 365, col. 2.

Bestor and Tycko 1996 demonstrates why Gunzburg et al. is not relevant to the invention. Gunzburg et al. does not address the host defense mechanism at all or that fact that vectors had been shown to be actively silenced by methylation. Fifth Bleck Decl., ¶ 8.

- Garrick et al. 1998 (attached at Tab 2 to the Fifth Bleck Decl.) provide evidence on repeat-induced gene silencing in mammals. Fifth Bleck Decl., ¶ 8. Garrick used a lox/cre system to analyze the effect of copy number on transgene expression. Fifth Bleck Decl., ¶ 8; Garrick found that "reduction in copy number results in a marked increase in expression of the transgene and is accompanied by decreased chromatin compaction and decreased methylation at the transgene locus." Fifth Bleck Decl., ¶ 8; Garrick p. 56, col. 1., p. 58. Again, this paper provides evidence that the state of the art was that increasing copy number leads to methylation and inactivation of transgenes. Id. The vector construct was not a retroviral vector, but this data is directly relevant to inactivation of an introduced transgene. Id. As Bestor and Tycko 1996 indicated, the host defense mechanism is triggered by multiple copies of invasive sequences. Id. The transposon system used in this paper and retroviral vectors are both invasive sequences. Id.

- Cherry et al. 2000 (attached at Tab 3 to the Fifth Bleck Decl.) is co-authored by two of the leading scientists in the field, Dr. David Baltimore and Dr. Rudy Jaenisch. Fifth Bleck Decl., ¶ 8. They also recognize the role of methylation in the inactivation of proviral genes. Id. They state:

> DNA methylation is thought to be a general mechanism used by cells to silence

> foreign DNA and may be involved in the cell defense against transposable elements (39). DNA methylation has also been associated with the repression of gene expression and the silencing of viral control elements (2, 14, 38). Exogenously introduced retroviruses silenced in vitro and in vivo can be reactivated by treatments that result in genome wide demethylation. In addition, transcriptionally silent endogenous retroviral elements are reactivated upon loss of genomic methylation in Dnmtl knockout mice (38). Therefore, DNA methylation is thought to causally repress expression of retroviral promoters in a variety of cell types."

Cherry, p. 7419, col. 1-2. Both methylation-dependent and methylation-independent mechanisms exist to control retroviral gene expression. Fifth Bleck Decl., ¶ 8; Cherry, p. 7425, col. 1.

- Mehtali et al. 1990 (attached at Tab 4 to the Fifth Bleck Decl.) conducted experiments that show that methylation of an introduced transgene increases with increasing copy number and that expression of the transgene decreases with increasing copy number after initially increasing. Fifth Bleck Decl., ¶ 8; See Table 1, p. 182. The vector construct was not a retroviral vector, but this data is directly relevant to inactivation of an introduced transgene. Id.

- Niwa et al. 1983 (attached at Tab 5 to the Fifth Bleck Decl.) postulated that that there are two independent mechanisms that block expression from newly acquired retroviral vectors. Fifth Bleck Decl., ¶ 8; Niwa, See Abstract, p. 1105. The first mechanism operates in undifferentiated cells to block expression of M-MuLV and other exogenously acquired viral genes, such as SV40 and polyoma virus, and does not depend on DNA methylation. Id. The second mechanism relates only to differentiated cells and represses expression of genes in which DNA is methylated. Id. This paper further serves to demonstrate why the Examiner's reliance on Gunzburg et al. is inappropriate. Fifth Bleck Decl., ¶ 8. Newly acquired retroviral vectors are treated by cells in a different manner from proviral sequences that have been integrated into the genome in the distant

past and essentially become endogenous. Id.

- Svoboda et al. 2000 (attached at Tab 6 to the Fifth Bleck Decl.) examines the expression of retroviral vectors in foreign species. Fifth Bleck Decl., ¶ 8. The vectors are subject to cell-mediated control at the transcriptional and posttranscriptional levels. Fifth Bleck Decl., ¶ 8; Svoboda, Abstract, p. 181. Of main importance is cell transcriptional regulation, which can lead to proviral silencing. Fifth Bleck Decl., ¶ 8; Svoboda p. 181, col. 2. The authors note that all of the data so far point to the important role of methylation in provirus silencing in general and that strategies for preventing methylation should contribute to more efficient gene transfer in the future. Fifth Bleck Decl., ¶ 8; Svoboda p. 186, col. 2. Again, the state of the art was that newly acquired retroviral vectors are subject to silencing by methylation. Fifth Bleck Decl., ¶ 8. This is in direct contrast to the Examiner's conclusions based on Gunzburg et al. Id.

- Ellis and Pannell 2001 (attached at Tab 7 to the Fifth Bleck Decl.) also examine retrovirus silencing. Fifth Bleck Decl., ¶ 8. They state that inclusion of appropriate regulatory elements may not be sufficient because the vectors are frequently silenced and that a better understanding of the mechanism of vector silencing is needed. Fifth Bleck Decl., ¶ 8; Ellis p. 17, col. 1-2.

- Challita and Kohn 1994 (attached at Tab 8 to the Fifth Bleck Decl.) provide data that shows that lack of expression following retroviral transduction is due to methylation. Fifth Bleck Decl., ¶ 8. As stated by the authors: "Methylation of cytosine residues has been shown to be associated with suppression of gene expression and, in certain circumstances, with the silencing of viral control elements (6). The MoMuLV-LTR is completely inactive in embryonic stem and embryonic carcinoma cell lines, and the inactivity is accompanied by de novo methylation of the proviral sequences (7, 8). Moreover, methylation has been detected in association with the MoMuLV-LTR transcriptional inactivity in fibroblasts in vitro (9) and in vivo (2)." Fifth Bleck Decl., ¶ 8; Challita, p. 2567. As shown by Ellis and Pannell (Tab 6 of Fifth Bleck Decl.), these

problems still had not been solved by 2001, even when regulatory elements other than the retroviral LTR are used. Fifth Bleck Decl., ¶ 8.

These references establish that at the time of the claimed invention the state of the art was that: 1) cells have a host defense mechanism that inactivates newly introduced, invading sequences such as retroviral vectors; 2) the host defense mechanism operates by methylation of the invading sequences, which causes transcriptional inactivation of the sequences; 3) transcriptional inactivation by methylation leads to reduced expression from retroviral vectors; 4) the inactivation may be triggered by structures formed during integration of the retroviral vectors; and 5) the presence of multiple repeats of an invading sequence such as a retroviral vector triggers methylation and inactivation. Fifth Bleck Decl., ¶ 9.

These facts establish the state of the art. Applicants respectfully submit the totality of the prior art must be considered, and that proceeding contrary to the accepted wisdom in the art is evidence of non-obviousness. MPEP §2145. Applicants further submit that predictability as discussed in KSR encompasses the expectation that prior art elements are capable of being combined, as well as the expectation that the combination would have worked for its intended purpose. An inference that a claimed combination would not have been obvious is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314 (Fed. Cir. 2009). With respect to the instant application, the prior art teaches that the host defense mechanism in cells causes inactivation by methylation of invading sequences, such as those contained on retroviral vectors, and especially where multiple copies are introduced. This teaching undermines the reason for combination proffered by the Examiner – namely that increasing the number of integrations past, for example, 8 integrations as taught in Mathor (the number where maximum expression was observed in that reference) would increase expression. The prior art teaches that expression would likely be lower due to inactivation by methylation.

3, 4, and 5. The remaining rejections are also defective.

The Examiner also made the following rejections:

3) Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al., in view of Schroder et al.;

4) Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Primus et al. and Kolb et al.;

5) Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Naldini et al.

The additional citations in these rejections of Schroder, Primus and Kolb, and Naldini do not cure the defects noted above for the rejection over Mathor in view of Burns, Felts, Schott, and Persons. In particular, the additional references do not address the scientific deficiencies in the Examiner's arguments described in detail above or rebut or address Applicant's arguments regarding the fact that the prior art as a whole teaches away from the claimed invention. Accordingly, each of these rejections should be withdrawn.

CONCLUSION

All grounds of rejection and objection of the Office Action of May 13, 2010 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 662-1277.

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